EXEM FOAM- air polymer-type a intrauterine foam
GISKIT B.V.

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use EXEM® FOAM safely and effectively. See full prescribing information for EXEM® FOAM.

EXEM FOAM (air polymer-type A) intrauterine foam

Initial U.S. Approval: 2019

INDICATIONS AND USAGE

ExEm ® Foam is an ultrasound contrast agent indicated for sonohysterosalpingography to assess fallopian tube patency in women with known or suspected infertility. (1)

DOSAGE AND ADMINISTRATION

- Confirm the patient is not pregnant prior to ExEm Foam administrations (2.1)
- Recommended dose is 2 mL to 3 mL of ExEm Foam by intrauterine infusion using a 5-Fr or larger catheter. Dose may be repeated in 2 mL to 3 mL increments, as needed, to achieve visualization of the fallopian tubes. Maximum total dose is 10 mL (2.2)
- See Full Prescribing Information for preparation and administration instructions. (2.3)

DOSAGE FORMS AND STRENGTHS

Intrauterine Foam, single-dose kit containing:

- one syringe with 5 mL clear Gel [polymer type A (hydoxyethyl cellulose), glycerin and purified water]
- one syringe with 5 mL Sterile Purified Water
- one Combifix ® Adaptor (coupling device) (3)

CONTRAINDICATIONS

- ExEm Foam is contraindicated in:
  - Pregnancy (4)
  - Patients with known or suspected lower genital tract inflammation or infection (4)
  - Patients who have had a gynecologic procedure within the last 30 days (4)
  - Patients with vaginal bleeding (4)
  - Patient with known or suspected reproductive tract neoplasia. (4)

WARNINGS AND PRECAUTIONS

- Risk for fetal harm: Confirm that the patient has a negative pregnancy test within the 24 hours before ExEm Foam administration and confirm that the patient is in the pre-ovulatory phase of her menstrual cycle (cycle days 6 through 11). (4, 5.1)
- Risk for Post-Procedure Gynecologic Infections: Do not use in contraindicated situations even if the patient is receiving antimicrobial therapy. (4, 5.2)

ADVERSE REACTIONS

Common adverse reactions are: pelvic and abdominal pain; vasovagal reactions and associated symptoms such as nausea and faintness; and post-procedure spotting. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact ExEm Foam Inc. at 1-844-963-EXEM (1-844-963-3936) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.
See 17 for PATIENT COUNSELING INFORMATION.

Revised: 11/2019

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

ExEm ® Foam is indicated for sonohysterosalpingography to assess fallopian tube patency in women with known or suspected infertility.

2 DOSAGE AND ADMINISTRATION

2.1 Important Pre-Administration Information

To ensure that the patient is not pregnant prior to ExEm Foam administration *[see Contraindications (4) and Warnings and Precautions (5.1)]:*

- Confirm that the patient has a negative pregnancy test within the 24 hours before ExEm Foam administration .
- Confirm the patient is in the pre-ovulatory phase of her menstrual cycle (cycle days 6 through 11).

2.2 Recommended Dosage

- The recommended initial dose of ExEm Foam is 2 mL to 3 mL by intrauterine infusion using a 5-Fr or larger catheter with luer connection.
- The dose may be repeated in increments of 2 mL to 3 mL, as needed, to achieve visualization of the

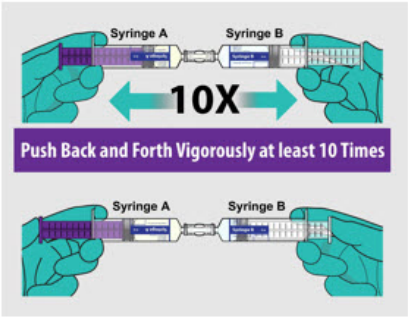
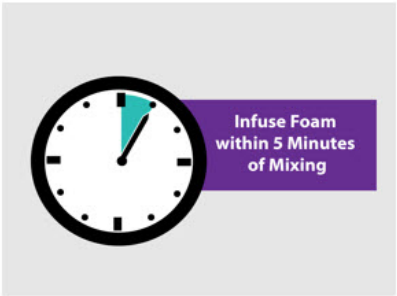
fallopian tubes.
- Maximum total dose is 10 mL.

2.3 Preparation and Administration

The ExEm Foam kit includes the following components:
- Syringe A containing 5 mL clear Gel [polymer type A (hydoxyethyl cellulose), glycerin and purified water]
- Syringe B containing 5 mL Sterile Purified Water
- Combifix Adapter (coupling device)

Preparation
- Examine the package and **do not use if** package has been previously opened or damaged.
- Ensure the kit is at room temperature.
- Handle products following aseptic practices (e.g. sterile gloves).
- Generate foam by mixing Syringe A (Gel) with Syringe B (Sterile Purified Water) included in the package as described in **Figure 1.**
- Infuse foam within 5 minutes of reconstitution.

FIGURE 1: Reconstitution of ExEm Foam

• Unscrew and discard the caps from each syringe when ready to prepare the foam. • Push and screw Syringe A to one end of the Combifix Adapter. • Push and screw Syringe B to the other end of the Combifix Adapter. • Make sure these syringes are attached tightly to avoid loss of liquid when mixing. • Push the plunger of one syringe vigorously to transfer, and begin mixing the contents from one syringe to the other syringe. **Repeat this process at least 10 times.** • The reconstituted foam is completely milky white (opaque) in color • After mixing, transfer all of the foam into one syringe, then disconnect the adapter and other syringe. • Approximately 10 mL of ExEm Foam is created by mixing Syringe A of clear Gel with Syringe B of Sterile Purified Water.	 

• **Infuse within 5 minutes of mixing** to ensure adequate imaging.	

Administration

- Administer through a 5-Fr or larger catheter with luer connection only. If there is resistance when infusing foam use a larger catheter. Do not infuse forcefully.
- Infuse 1 mL of foam to confirm proper placement of the catheter tip in the cervix and access to the uterine cavity.
- Slowly infuse 2 mL to 3 mL of the foam at a time to avoid patient discomfort.
- Discard unused portion after use.

2.4 Imaging Guidance

Conduct transvaginal ultrasound imaging in accordance with ultrasound manufacturer recommendations.

ExEm Foam in the fallopian tube will appear as an echogenic line along the length of the tube on the image.

A fallopian tube is classified as **patent** if ExEm Foam is observed to pass from the tube and spill into the peritoneal cavity. The tube will appear as a thin, bright line.

A fallopian tube is classified as **occluded** if ExEm Foam is not observed to pass from the tube and spill into the peritoneal cavity. As secondary findings, (1) there may be no bright line due to no flow into the fallopian tube, or (2) the tubal lumen may appear distended and contrast flow might be observed only in the intramural or isthmic part of the tube.

3 DOSAGE FORMS AND STRENGTHS

Intrauterine Foam, single-dose kit containing:

- Syringe A: one syringe with 5 mL clear Gel [polymer-type A (hydoxyethyl cellulose), glycerin and purified water]
- Syringe B: one syringe with 5 mL Sterile Purified Water
- One Combifix Adaptor (coupling device)

When prepared as directed ExEm Foam will contain between 10,000 to 127,000 bubbles per mL.

4 CONTRAINDICATIONS

ExEm Foam is contraindicated for use in:

- Pregnancy *[see Warnings and Precautions (5.1)]* .
- Patients with known or suspected lower genital tract inflammation or infection *[see Warnings and Precautions (5.2)]*.
- Patients who have had a gynecologic procedure within the last 30 days *[see Warnings and Precautions (5.2)]*.
- Patients with vaginal bleeding
  - Due to the risk of intravasation of ExEm Foam as a result of exposure of the endometrial vessels during bleeding, and
  - Due to the potential risk of endometriosis as a result of seeding the peritoneum with endometrial tissue.
- Patients with known or suspected reproductive tract neoplasia due to the risk of peritoneal spread of neoplasm .

5 WARNINGS AND PRECAUTIONS

5.1 Risk for Fetal Harm

ExEm Foam is contraindicated for use in pregnancy due to the potential risk of fetal harm from an intrauterine procedure. To ensure that the patient is not pregnant prior to ExEm Foam administration, confirm that the patient has a negative pregnancy test within the 24 hours before ExEm Foam administration and confirm that the patient is in the pre-ovulatory phase of her menstrual cycle (cycle days 6 through 11) *[see Contraindications (4)]*.

5.2 Risk for Post-Procedure Gynecologic Infections

There is a risk of post-procedure gynecological infections when ExEm Foam is used in sonohysterosalpingography. ExEm Foam is contraindicated for use in patients with known or suspected genital tract inflammation or infections (e.g. including pelvic inflammatory disease (PID) or suspected sexually transmitted disease) even if the patient is receiving antimicrobial therapy. ExEm Foam is contraindicated in patients who have had a gynecologic procedure within the past 30 days (e.g. curettage or conization) due to the risk of post-procedure infections *[see Contraindications (4) and Adverse Reactions (6.2)]* .

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug may not reflect the rates observed in practice.

The common adverse reactions associated with ExEm Foam when used as indicated in sonohysterosalpingography are: pelvic and abdominal pain; vasovagal reactions and associated symptoms such as nausea and faintness; and post-procedure spotting.

6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of (air polymer-type A) intrauterine foam outside of the United States. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Gynecologic Infections: pelvic inflammatory disease, salpingitis, and tubo-ovarian abscess

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

ExEm Foam is contraindicated for use in pregnancy due to the potential risk to the fetus from an intrauterine procedure *[see Contraindications (4) and Warnings and Precautions (5.1)]* . There are no available data on the use of ExEm Foam in pregnant women. Animal reproduction studies have not been conducted with ExEm Foam.

8.2 Lactation

Risk Summary

There are no data on the presence of the components used to generate ExEm Foam (glycerin and hydroxyethyl cellulose) in human milk, the effects on the breastfed infant, or the effects on milk production. No adverse effects in breastfed infants are anticipated following maternal administration of

ExEm Foam, based on the wide safety margin for glycerol in infants and the expected negligible absorption of hydroxyethyl cellulose *[see Clinical Pharmacology (12.3)]*. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for ExEm Foam and any potential adverse effects on the breastfed infant from ExEm Foam or from the underlying maternal condition.

8.3 Females and Males of Reproductive Potential

Confirm that the patient has a negative pregnancy test within the 24 hours before ExEm Foam administration *[see Dosage and Administration (2.1) and Use in Specific Populations (8.1)]*.

8.4 Pediatric Use

The safety and effectiveness of ExEm Foam have not been established in pediatric patients.

11 DESCRIPTION

ExEm Foam (air polymer-type A) intrauterine foam, is an ultrasound contrast agent. It is provided to the user for preparation as a single-dose kit containing:

- 5 mL sterile clear Gel [polymer-type A (80.97 mg hydoxyethyl cellulose), 434.80 mg glycerin 85%, and purified water]; with a pH of 6 to 7.5.
- 5 mL Sterile Purified Water; with a pH of 6 to 7.5.

After preparation, ExEm Foam is a milky-white, water-soluble intrauterine foam with an osmolality of approximately 462 mOsm and will contain between 10,000 to 127,000 bubbles per mL with a median size of 45.6 to 60.6 micrometers (for bubbles between 20 to 200 micrometers).

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

ExEm Foam (air polymer-type A) intrauterine foam is formed by mixing the clear Gel [polymer-type A (hydoxyethyl cellulose), glycerin, and purified water] with air and Sterile Purified Water, creating an echogenic contrast agent. When visualized with ultrasound, the foam appears echogenic or bright within the fallopian tubes and peritoneal cavity.

12.2 Pharmacodynamics

ExEm Foam has no known pharmacological activity.

12.3 Pharmacokinetics

Assuming that a full 10 mL of ExEm Foam is used, and all glycerol is absorbed, the normal fasting endogenous glycerol plasma levels would not be affected. No literature data is found on absorption of hydroxyethyl cellulose (HEC) from the female reproductive tract and peritoneum. HEC is poorly permeable across GI epithelial mucosa; therefore, HEC is expected to exhibit very low permeability after administration and to produce negligible HEC systemic exposure.

The metabolism and excretion of HEC are not known.

13 NONCLINICAL TOXICOLOGY

No nonclinical toxicology studies have been conducted with ExEm Foam. Glycerol-hydroxyethyl cellulose (HEC) Gel is not genotoxic (Ames test) or cytotoxic (mouse lymphoma L5178Y TK+/- assay).

14 CLINICAL STUDIES

Clinical studies reported in the scientific literature have assessed the performance of sonohysterosalpingography with ExEm Foam (a technique referred to as HyFoSy) for the diagnosis of tubal patency in women with infertility. The studies used laparoscopy with chromotubation as the reference standard.

Study A compared 2D- and 3D-HyFoSy to previous laparoscopy with chromotubation in 50 women (median age 35 years) with at least 12 months of infertility (median duration of infertility 28 months). The women were randomly assigned to either HyFoSy with 2D imaging or HyFoSy with 3D imaging. The operator performing HyFoSy was blinded to the laparoscopy results. For 2D imaging, the proportion of fallopian tubes correctly identified as occluded was 80% and the proportion of tubes that were correctly identified as patent was 92%. For 3D imaging, the proportion of tubes correctly identified as occluded was 98% and the proportion of tubes that were correctly identified as patent was 91%.

Study B compared the diagnostic performance of HyFoSy with ExEm Foam using both 2D/3D-sonohysterosalpingography (2D/3D-HyFoSy) and 2D/3D-HyFoSy with high-definition flow Doppler enhancement (2D/3D-HDF-HyFoSy), to the reference standard of laparoscopy with chromotubation to establish the patency of the tubes. The study evaluated 132 women (259 fallopian tubes) with history of primary or secondary infertility who were consecutively enrolled over a period of 2 years. The mean age was 32 years and the mean duration of infertility was 2.6 years. The performance of 2D/3D-HyFoSy was similar to that of 2D/3D-HDF-HyFoSy. The performance estimates in Study B were numerically similar to those reported in Study A.

16 HOW SUPPLIED/STORAGE AND HANDLING

Supplied

ExEm Foam is supplied as a single-dose kit, NDC 73254-310-01. Each kit contains:

- Syringe A: One sterile syringe containing 5 mL of clear Gel [polymer-type A (hydoxyethyl cellulose), glycerin and purified water
- Syringe B: One sterile syringe containing 5 mL of Sterile Purified Water
- One sterile Combifix Adaptor (coupling device)

Storage and Handling

Store the kit and components at controlled room temperature between 20° to 25°C (68° to 77°F); [see USP Controlled Room Temperature]; excursions permitted at 15° to 30°C (59° to 86°F). Do not store in refrigerator. Do not freeze.

17 PATIENT COUNSELING INFORMATION

Risk for Post-Procedure Gynecologic Infections

Patients should be counseled regarding the risk of post-procedure gynecologic infections. Instruct patients to report to their healthcare provider any continued pelvic and abdominal pain, significant vaginal discharge and/or fever post-procedure *[see Warnings and Precautions (5.2) and Adverse Reactions (6.2)]* .

Abdominal and Pelvic Pain

Inform patients of the potential for transient abdominal and pelvic pain during and after ExEm Foam sonohysterosalpingography *[see Adverse Reactions (6.1)]*

Manufactured for and Distrbuted By: ExEm Foam Inc.
228 East 45 th Street, Suite 9E
New York, NY 10017

ExEm ® is a registered trademark of GISKIT B.V.

PRINCIPAL DISPLAY PANEL - Kit Carton

Rx only
NDC 73254-310-01

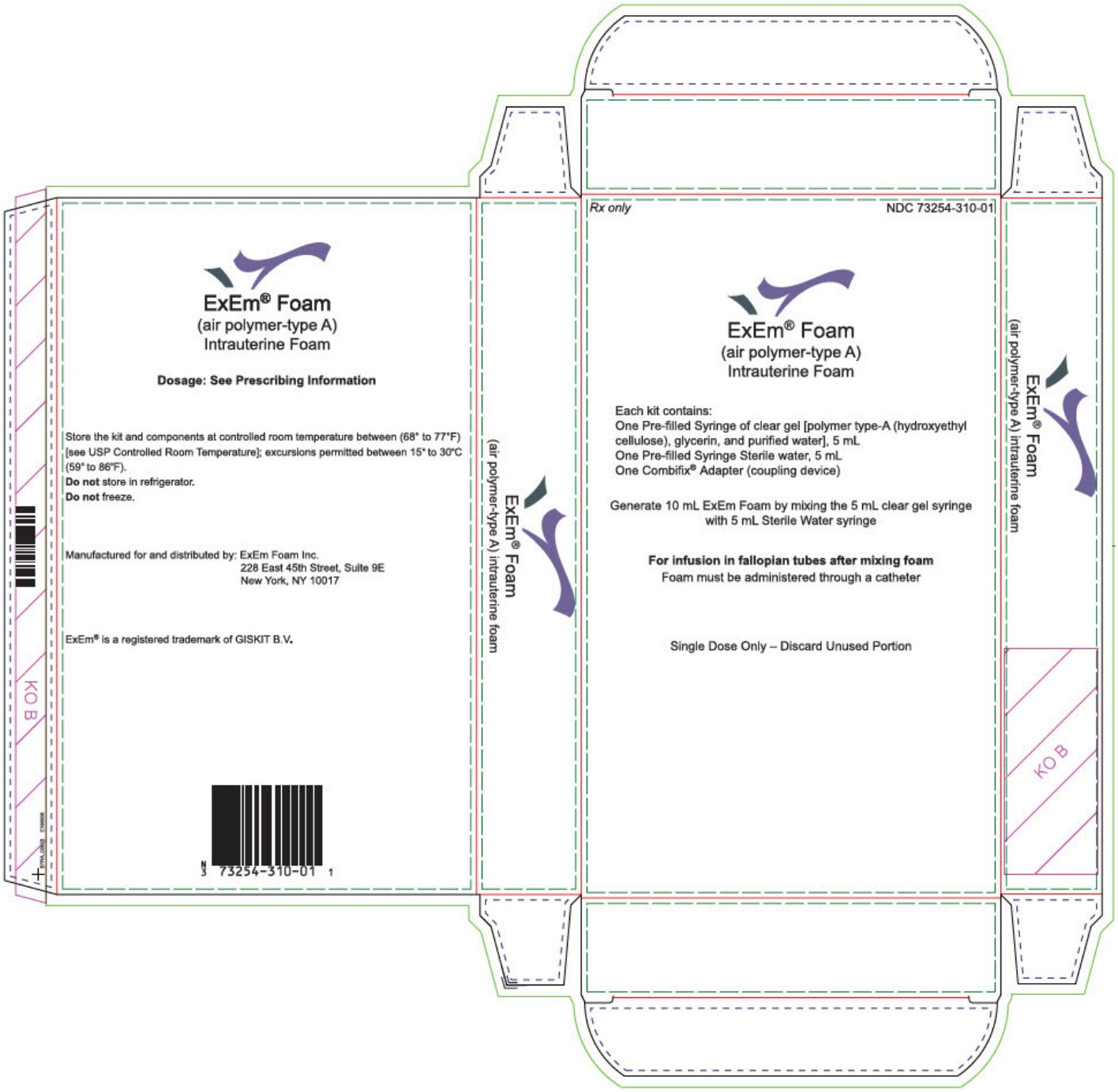
ExEm ® Foam
(air polymer-type A)
Intrauterine Foam

Each kit contains:
One Pre-filled Syringe of clear gel [polymer type-A (hydroxyethyl cellulose), glycerin, and purified water], 5 mL
One Pre-filled Syringe Sterile water, 5 mL
One Combifix ® Adapter (coupling device)

Generate 10 mL ExEm Foam by mixing the 5 mL clear gel syringe with 5 mL Sterile Water syringe

For infusion in fallopian tubes after mixing foam
Foam must be administered through a catheter

Single Dose Only – Discard Unused Portion



EXEM FOAM

air polymer-type a intrauterine foam kit

Product Information			
Product Type	HUMAN PRESCRIPTION DRUG	**Item Code (Source)**	NDC:73254-310

Packaging				
#	**Item Code**	**Package Description**	**Marketing Start Date**	**Marketing End Date**
1	NDC:73254-310-01	1 in 1 CARTON; Type 0: Not a Combination Product	10/16/2020	

Quantity of Parts		
Part #	**Package Quantity**	**Total Product Quantity**
Part 1	1 SYRINGE, PLASTIC	5 mL
Part 2	1 SYRINGE, PLASTIC	5 mL

Part 1 of 2

SYRINGE A

hydroxyethyl celluose, glycerin gel

Product Information	
Route of Administration	INTRAUTERINE

Active Ingredient/Active Moiety		
Ingredient Name	**Basis of Strength**	**Strength**
GLYCERIN (UNII: PDC6A3C0OX) (GLYCERIN - UNII:PDC6A3C0OX)	GLYCERIN	434.8 mg in 5 mL
HYDROXYETHYL CELLULOSE (5500 MPA.S AT 2%) (UNII: M825OX60H9) (HYDROXYETHYL CELLULOSE (5500 MPA.S AT 2%) - UNII:M825OX60H9)	HYDROXYETHYL CELLULOSE (5500 MPA.S AT 2%)	80.97 mg in 5 mL

Inactive Ingredients	
Ingredient Name	**Strength**
WATER (UNII: 059QF0KO0R)	

Packaging				
#	**Item Code**	**Package Description**	**Marketing Start Date**	**Marketing End Date**
1		5 mL in 1 SYRINGE, PLASTIC; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA212279	10/16/2020	

Part 2 of 2

SYRINGE B

sterile purified water liquid

Product Information

Route of Administration	INTRAUTERINE

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
WATER (UNII: 059QF0KO0R) (WATER - UNII:059QF0KO0R)	WATER	5 mL in 5 mL

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1		5 mL in 1 SYRINGE, PLASTIC; Type 0: Not a Combination Product		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA212279	10/16/2020	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA212279	10/16/2020	

Labeler - GISKIT B.V. (409111437)

Establishment

Name	Address	ID/FEI	Business Operations
Labor L&S AG		314929072	analysis(73254-310)

Establishment

Name	Address	ID/FEI	Business Operations
Klosterfrau Berlin GmbH		316067594	manufacture(73254-310) , label(73254-310) , sterilize(73254-310) , analysis(73254-310)

Establishment

Name	Address	ID/FEI	Business Operations
A+ Secure Packaging, LLC (d/b/a Cardinal Health Packaging Solutions)		963589036	label(73254-310) , pack(73254-310)

Revised: 5/2020 GISKIT B.V.